

FDA Advisory Committee Briefing Document

Cardiovascular and Renal Drugs Advisory Committee

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Safety Considerations in the Development of Ultrasound Contrast Agents

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1. Introduction

Ultrasound contrast agents are "microbubble" (or "microsphere") drugs that are injected into the vascular system in order to improve the diagnostic information obtained from ultrasound-based images. The ultrasound contrast agents approved by the FDA (Definity and Optison) are both used in ultrasound of the heart, or echocardiography, and assist in the diagnosis of cardiac conditions. However, ultrasound contrast agents are undergoing clinical investigations for use in other conditions and settings, such as the detection of stenoses within the peripheral vasculature and the detection of liver abnormalities.

Ultrasound contrast agents consist of a core gas surrounded by an outer layer ("shell") of molecules. Both Definity and Optison contain perflutren (octafluoropropane) as the core gas but the two agents differ in the outer molecular shell. The Definity shell consists of phospholipids and the Optison shell consists of albumin. The microbubble size of both agents is generally similar to that of a red blood cell, with a very small proportion of microbubbles larger than 10 microns. Hence, following injection into a vein, the smallest microbubbles travel through the pulmonary vasculature and into the left heart while the largest bubbles are thought to embolize within the pulmonary vasculature. The microbubbles within the left heart can be detected by an ultrasound probe since the bubbles are compressible within the sound field. The altered echo signal helps to increase the contrast between the blood pool and the heart surface, a change that may improve the diagnostic performance of the ultrasound examination. Definity and Optison are approved for the same indication, "for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border." FDA has invited the Definity and Optison manufacturers to participate in this advisory committee.

FDA has also invited the manufacturer of a third ultrasound contrast agent, SonoVue, to participate in the advisory committee. SonoVue, a product marketed in Europe, consists of a core gas of sulphur hexafluoride and an outer shell of specific phospholipids. SonoVue is approved in Europe for use in echocardiography as well as for use in examination of the peripheral vasculature and for vascularity assessments of liver and breast lesions.

The uniqueness of the physical and chemical properties of the ultrasound contrast agents, the technicalities of the ultrasound field and its rapid technical advances, combined with the unique design considerations for clinical studies of diagnostic imaging agents have all presented special challenges in the clinical development and optimal use of these agents. For example, the premarketing clinical studies of these agents were generally designed to use "patients as their own controls" and the eligibility criteria largely excluded patients with important comorbidities, such as pulmonary dysfunction or severe heart failure. However, the post-marketing experience suggests that the agents are importantly used in patients with severe underlying comorbidities and these patients account for a disproportion of the reported adverse reactions to the agents.

Additionally, preclinical data have importantly influenced the development of these agents and these animal studies have sometimes revealed safety signals of unclear import for use of the agents in humans. Nevertheless, animal study findings were directly responsible for the initial determination that Definity and Optison pose unacceptable risks for systemic arterial

microbubble embolization in patients with right to left shunts. Accumulating animal study data have also presented models for acute serious cardiopulmonary reactions to the agents. The clinical meaningfulness of some of the reactions detected in various animal species is a special challenge for review of these data.

This advisory committee is convened to provide a public forum for review of the history of the currently marketed ultrasound contrast agents, to obtain opinions from the advisors regarding safety considerations in the development of these agents and to begin to familiarize the committee members with the review of diagnostic imaging agents. FDA is currently reviewing multiple diagnostic imaging agents and anticipates presentation of some of these agents to advisory committees over the next many months.

This advisory committee will not discuss any specific contrast agent with respect to unique regulatory considerations of safety and/or efficacy. Instead, the experience with these agents will be detailed by the manufacturers of the marketed products in order to prompt a discussion that should assist in the future development of these agents.

This meeting was prompted, in part, by recent safety considerations for the approved products that resulted in label changes and the development of risk management plans. This experience is summarized below and followed by a bibliography (and reprints for advisory committee members) of background publications.

2. Goals of This Advisory Committee

The goals of this advisory committee are:

a. Visibility:

Specifically, to provide a summary of the development of the currently marketed ultrasound contrast agents, with a focus upon the "lessons learned" in the preclinical (animal) and clinical development of these agents, as well as the postmarketing experience.

b. Stimulate discussion:

To obtain perspectives from the committee members regarding the types of preclinical and clinical data essential to characterize the safety of the ultrasound contrast agents, especially as it applies to new uses of the approved contrast agents as well as the development of new agents.

c. Anticipate subsequent presentations:

To refamiliarize the advisory committee members with the review of diagnostic imaging agents, in anticipation of subsequent, product-specific discussions. The last discussion of any imaging agent at any FDA advisory committee was over three years ago and multiple new cardiovascular imaging agents are on the horizon for marketing consideration.

3. Topics for Questions and Discussion

FDA anticipates the following topics and questions to stimulate discussion:

1. Discuss the implications of preclinical (animal) data for the clinical development of ultrasound contrast agents.
 - a. Discuss the value of specific animal species, e.g., pig versus dog, including limitations and strengths of the models.
 - b. To what extent, if any, should contrast agents be studied in animal models of disease (such as animal models of myocardial ischemia or pulmonary dysfunction)?
2. The echocardiographic contrast agents may ultimately be used in clinical situations that importantly differ from those used in premarket clinical studies. Discuss the study design considerations that will help obtain important safety data prior to FDA approval of an ultrasound contrast agent.
 - a. Consider phase 3 studies that use eligibility criteria designed predominantly to optimize the assessment of diagnostic efficacy. These studies may exclude subjects with complex underlying conditions that may increase diagnostic variability. Discuss options for obtaining premarketing clinical data pertinent to assessing risks for the ultimate market population. To what extent do you regard these data as essential prior to market approval?
 - b. To what extent can studies that lack randomized control groups provide a thorough safety assessment?
3. What considerations would you regard as important in generalizing the safety findings from one ultrasound contrast agent to another one? Consider the chemical differences, the technique of administration (bolus versus infusion), animal and clinical data.
4. Based upon presentations and background information, what do you regard as the most important considerations in the characterization of the safety risks for ultrasound contrast agents?

4. Recent Safety Considerations for Ultrasound Contrast Agents

Major Points:

- Ultrasound Contrast Agents (Definity and Optison) are used to improve echocardiographic images of the left ventricle. Post-marketing reports and new animal data prompted major label changes for these products in October, 2007. These changes most notably included a boxed warning and contraindication for use of the products in certain patients with underlying cardiopulmonary conditions.
- The October, 2007 label changes were made based upon:
 - post-marketing spontaneous reports of ~ 200 serious adverse events shortly following administration of the products, including seven deaths. The reported reactions were generally similar to allergic reactions (hives, breathlessness, back pain) as well as reactions that appeared to be directly related to cardiac or pulmonary complications. These cardiac or pulmonary complications included problems such as cardiac arrest, heart rhythm problems, hypotension and hypoxemia. Additionally, some reactions also included seizures or loss of consciousness.
 - animal study findings appeared to duplicate the pattern of serious cardiopulmonary reactions observed in humans; administration of Optison and SonoVue was reported to cause transient but marked pulmonary hypertension and systemic hypotension in pigs at clinically relevant doses of the contrast agents. FDA notes that the pig model has been reported as especially important for modeling human outcomes. For example, the recent experience with contaminated heparin showed that, of the animal species tested, only the pig responded in a pattern similar to humans.
 - the precedent for SonoVue. SonoVue is a product marketed in Europe that, subsequent to serious adverse event reports, was temporarily suspended in marketing; marketing was resumed with contraindications for its use in patients with recent acute coronary syndromes, clinically unstable ischemic cardiac disease, acute cardiac failure, class 3/4 cardiac failure or severe rhythm disorders.

The changes were also made in the context of deficiencies, including the lack of available pulmonary hemodynamic data in humans, a premarketing database that generally excluded patients with unstable cardiopulmonary conditions, the lack of a systematic risk assessment and management plan as well as failure of a manufacturer to initiate an important post-marketing clinical study commitment to assess its product's safety.

- Post-marketing reports of serious adverse reactions over the recent past have mainly cited the use of Definity, since Optison was not marketed between November, 2005 and late October, 2007.

- Following the October, 2007 label changes, FDA received reports from physicians who were especially concerned about the extent of Optison and Definity label changes, especially the contraindications pertaining to certain unstable patients. The physicians noted that the contrast agents may provide essential diagnostic information in some of these patients. FDA also obtained two published reports that suggested Optison and SonoVue administration did not cause pulmonary or systemic hypotension, when pulmonary hemodynamics were monitored invasively.
- FDA has most recently been working with the Optison and Definity manufacturers to develop a risk assessment and management program. In addition to physician education and enhanced oversight of clinical studies and this program consists of two major studies. One is an observational study to be conducted using an administrative database in which mortality will be compared between critically ill patients who receive a contrast-enhanced echocardiogram and critically ill patients who undergo echocardiography without contrast. The second study will obtain pulmonary hemodynamic data from patients who are undergoing right heart catheterization as well as contrast-enhanced echocardiography.
- FDA has finalized the risk management plan with the manufacturer of Definity and has approved labeling changes that remove most of the contraindications cited in the October, 2007 modification, as well as focused monitoring procedures upon patients with underlying pulmonary hypertension or unstable cardiopulmonary conditions. FDA is working with the manufacturer of Optison to effect similar changes to the label and to finalize a risk assessment and management program.
- FDA remains concerned about the accumulating safety data pertaining to marketed ultrasound contrast agents and the labels for these products continue to contain a boxed warning that highlights the risk for serious cardiopulmonary reactions.
- Since the label revision of October, 2007, FDA has received reports of four additional deaths that occurred following the administration of Definity. One patient with severe congestive heart failure died within five minutes following Definity administration. A second patient with a history of coronary artery disease and hypertension developed "infusion reaction" symptoms and cardiac arrest within 30 minutes of perflutren administration. Another patient reportedly died approximately 10 minutes after Definity but the details of the patient's underlying condition were not described. Another patient with underlying pulmonary hypertension died approximately two hours after a Definity injection. In addition to these events, FDA has received a report of a patient who had a cardiac arrest within minutes after a Definity injection; this patient was revived.

5. Bibliography

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